NIAID Workshop
Development of Guillain Barre Syndrome Following *Campylobacter* Infection

Natcher Conference Center, NIH
Bethesda, MD, USA
August 26-27, 1996

Guillain Barre Syndrome (GBS) is a rare disorder, afflicting about 1 person in 100,000. Yet, since the decline in the number of polio cases, it represents the most common cause of acute neuromuscular paralysis. It is more common in Japan and China than in North America or Europe and it affects both sexes of any age. Symptoms range from weakness and tingling sensations in the legs to spread to the arms and upper body. While most patients recover with no, or minor, long term effects, total paralysis and the need for ventilatory assist and death can result.

In about two-thirds of cases, GBS is preceded a few days or weeks by a mild respiratory or intestinal infection. The organism most commonly proven to be associated with the development of GBS is *Campylobacter jejuni. C. jejuni* has become the leading cause of gastroenteritis in the developed world and is often acquired by ingestion of infected poultry products. GBS is thought to arise as a result of the production of antibody to bacterial sugar-containing surface antigen(s) that, due to molecular mimicry, cross-react with the myelin sheath and the axons of nerve cells. The ganglioside GM1 on nerve fibers seems to be a target for these antibodies, although other gangliosides may also be involved. Antibody and/or cell mediated immune reactions are believed to produce degeneration of the nerve or interruption of neurotransmission.

The purpose of this workshop was to explore the relationship between *C. jejuni* infection and the development of GBS. Scientists studying this problem from around the world were invited to present their latest data. Represented were the disciplines of microbiology, neurology, cell biology, immunology, and genetics. Topics for discussion included: the identification of the surface antigens of *C.jejuni* linked to GBS, the pathology of GBS, the identification of the target molecules on nerves attacked by anti-bacterial antibodies, animal models for GBS, possible interventions to prevent the develoment of GBS or its serious sequelae, and the implications of these findings on the development of a vaccine against *C. jejuni*.

Additional support for this meeting was provided by the National Vaccine Program Office (NVPO), theNational Institute for Neurological Diseases and Stroke (NINDS), the Food and Drug Administration (FDA), and the Department of Defense (DOD).

Workshop Conclusions and Recommendations

CONCLUSIONS

- With the decrease in polio, GBS has become the leading cause of acute flaccid paralysis in the world.
- GBS can probably result following a number of bacterial and viral infections. *Campylobacter jejuni* induced diarrheal disease is most often recognized as the precedent infection.
- The epidemiology of *Campylobacter* associated with GBS is complex and not well understood. The specific reservoirs for GBS-related strains are not known. There appears to be seasonality of infection (summer) in some countries but no seasonality of GBS. The patterns of association seem to be different in different parts of the world, as does the age of individuals developing GBS.
- There is an association of GBS with *C. jejuni* O serotypes 19 and 41. The strongest association has been with O19. For example, in the U.S., the risk of developing GBS following *C. jejuni* infection has been estimated as 1 in 1058, but as 1 in 158 following infection with *C. jejuni* O19.
- The structure of LPS is complex and unique in *Campylobacter*. These unique structures are evident in O side chains and core oligosaccharides. Often, portions of these structures resemble mammalian tissue gangliosides (molecular mimicry) and suggest a mechanism of immune damage to nerve fibers.
- The Department of Defense has developed, and is testing, a formalin-inactivated, whole cell, *Campylobacter jejuni* vaccine candidate. It is designated strain 81-176 and is a Lior type 5 (heat labile antigen based typing system) and O type 23/36.
- A significant amount of antibiotic resistance has been developing among the *Campylobacter*. This could lead to an increasing problem in treatment of human disease.
- The development of GBS is rare in children less than 2 years of age despite their susceptibility to *Campylobacter*. This may indicate that some maturation of the immune system is needed for GBS to manifest itself.
- The medical costs associated with *Campylobacter* induced GBS has been estimated by the USDA to be between $57 and $425 million per year in the U.S. Total costs, which include days of lost productivity, are estimated to be between $247 million and $1.8 billion per year.
- There is need for better standardized case definitions of acute motor axonal neuropathy (AMAN), acute motor-sensory neuropathy (AMSAN), acute inflammatory demyelinating polyneuropathy (AIDP), and Miller Fisher Syndrome (MFS) which are based on clinical, electrophysiologic, immunologic, and molecular data.

RECOMMENDATIONS

- The CDC surveillance for emerging diarrheal diseases should include *C. jejuni*, and *C. upsaliensis* in their plans. This would provide a better estimate of *Campylobacter* infection rates in this country.
- GBS (or more broadly defined acute flaccid paralysis cases) should be reportable by state health departments to the CDC. Current estimates are on the order of 1-4 cases of GBS per 100,000 population per year in the U.S. When combined with increased surveillance for *Campylobacter*, a much better picture of the epidemiology of the organism and its association with GBS should become apparent.
- Surveillance for GBS in targeted populations seems warranted, particularly in China (efforts are underway) where an increase in GBS is seen in the summer months and is associated with rural residence, and in Latin America (not underway) where cases of acute flaccid paralysis has not declined despite the tremendous decrease in polio cases.
- Studies should proceed on HLA typing of clinically well defined cases and controls in order to determine if there is a genetic component to host susceptibility to GBS.
- Standardized microbiological laboratory procedures are needed to insure isolation of *Campylobacter* strains associated with GBS. In particular *C. jejuni,* and *C. upsaliensis* should be looked for. The concept of viable but non-culturable *Campylobacter* should be examined.
- Serologic assays for diagnosis of *C. jejuni* infections need to be standardized and validated.
- A diagnostic test specific for various *Campylobacter* species is needed. It is likely that a large number of *Campylobacter* infections go unrecognized.
- An animal model for *Campylobacter* enteritis with ensuing GBS is urgently needed. A recently described ferret model for *Campylobacter*-induced enteritis may be useful. Mouse, rat, primate, chicken, and rabbit models for immune neuropathies are being examined and show promise but need to be developed further, perhaps by examining pathogen-free animals. The development of transgenic mice should also be considered.
- There should be a *Campylobacter* strain bank established in which bacterial strains isolated from patients who develop Guillain Barre Syndrome (or variants) can be deposited. These strains should be available to researchers in the field. There is a role that NIAID could play in the storage and distribution of strains from the NIAID repository.
- There is a need for standardized reagents, particularly monoclonal antibodies, that can be used to identify bacterial epitopes and which can be tested for their ability to react with different neural "targets". Well characterized reagents could also be distributed to researchers from an NIAID repository.
- A more complete LPS typing system that will include more of the strains now classified as "un-typeable" is needed. LPS typing should be complemented with a molecular typing system based on DNA restriction

length polymorphisms (RFLP), rRNA gene polymorphisms (ribotyping), or by polymorphism of other genes.

- Continuing effort is warranted to determine the LPS structures associated with the development of GBS. Identification of specific epitopes would be helpful. Since sialylated polysaccharides are suspect, a probe to detect the presence of sialyl transferase may be helpful in identifying GBS-associated strains.
- The mechanism of immune mediated nerve damage is poorly understood. The nature of the initial antigen-antibody reaction(s) which leads to damaging immune reactions which may involve cell mediated immunity, complement fixation, cytokine production, lymphocyte and macrophage infiltration, and breech of the blood-nerve barrier need to be better defined. Why gangliosides on nerves are particularly targeted or sensitive when compared to the same molecules found on other tissues is not known.
- Studies should be done to try to understand the variations noted in seasonality, or lack thereof, of GBS, and of the basis for the differences noted in the serotypes of *C. jejuni* that have been associated with the onset of GBS in different studies and in different regions of the world.
- The mechanism of intravenous immunoglobulin (IVIG) amelioration of GBS symptoms is not known. More research is needed with the aim of developing improved therapies.
- A mechanism to share preliminary information among scientists studying *Campylobacter* and/or associated GBS would be helpful in keeping this world-wide research community in contact. The ability to send such information to an Internet address, for example, that would be widely accessible was discussed. Posting of interesting new observations, information, or questions would facilitate research efforts by all involved. Information on DNA sequences, availability of new strains or reagents, new techniques, reservoirs of infection, structures of LPS or proteins, new typing methods, antibiotic resistance patterns, frequency of isolation of particular serotypes associated with GBS, epidemiology, etc. could be included in such an exchange.